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ABSTRACT

Although previous research with adult humans and nonhumans has suggested a relationship between sleep behavior and brain serotonin levels, no studies have been made of the relationship of normal children's or infants' sleep patterns to serotonin levels, tryptophan metabolism, or diet. This study investigates the relationship between dietary influences on behavioral organization in the human newborn after feeding and synthesis of the brain neurotransmitter serotonin. A total of 20 healthy full-term infants, appropriate for gestational age, were assigned to either tryptophan or valine feeding conditions. The tryptophan treatment group received a feed containing 33 mg/dl of tryptophan dissolved in a 10% glucose solution to maximize the carrier transport of tryptophan across the brain/blood barrier; the valine group received 50 mg/dl of valine, dissolved in a 5 percent glucose solution, to minimize tryptophan transport. Each infant was observed continuously for 3 hours after feeding, and records were made of the infants' state of consciousness at 1-minute intervals. Results suggested that modifying infant feeding preparations with tryptophan and carbohydrate mixtures produces an effect on newborn state behavior without disrupting such state characteristics as mode of onset through active sleep. Variations in serotonin levels in newborn brains thus appear to play a role in modulating the newborn's arousal behavior. (RH)

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DIETARY PRECURSORS OF SEROTONIN AND NEWBORN STATE BEHAVIOR

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This study examined the relationship between dietary influences on the synthesis of a brain neurotransmitter, serotonin, and behavioral organization in the human newborn after feeding. While traditional nutritional studies with newborns have focused on the effects of prenatal and postnatal malnutrition on the central nervous system and behavior (Winick, 1976; Brazelton, 1976), we have studied the short term influence of the composition of each meal on the synthesis of brain neurotransmitters and on behavior.

I will first briefly review for you influences on serotonin synthesis and the effects of serotonin on adult sleep. Then I will describe our study of the influences of dietary precursors of serotonin on newborn state behavior.

Serotonin Synthesis

The biosynthesis and degradation of serotonin is illustrated in the first slide.

Slide 1 about here

The rate-limiting step in the formation of serotonin is tryptophan's hydroxylation to 5-hydroxytryptophan, a process catalyzed by tryptophan hydroxylase. The 5-hydroxytryptophan is then decarboxylated to serotonin. Since the enzyme tryptophan hydroxylase is not fully saturated with its amino acid substrate at normal brain tryptophan levels, variations in these levels by modifying enzyme saturation control the overall rate of serotonin synthesis. Tryptophan, an essential amino acid, cannot be synthesized in the body; thus, the only source of this precursor for brain serotonin synthesis is

dietary tryptophan, consumed as such, or in much larger amounts as a constituent of protein. Once synthesized, the major mechanism for the metabolism of serotonin is degradation by monoamine oxidase with subsequent oxidation to 5-hydroxyindole acetic acid. Brain serotonin levels, then, are regulated in large part by the availability of the precursor amino acid tryptophan in plasma or serum.

The relationship between food consumption and serotonin synthesis is more complicated, as illustrated in the next slide.

Slide 2 about here

Tryptophan from dietary protein is transported across the blood-brain barrier by a carrier that also transports large neutral amino acids, including valine, leucine, isoleucine, tyrosine, methionine, and phenylalanine. For this reason, competition for carrier sites limits the entry of tryptophan into the brain. The ratio of the concentration of tryptophan to the concentration of competing large neutral amino acids increases when pure tryptophan is fed; it also rises when glucose is fed, because insulin facilitates the degradation of leucine, isoleucine, and valine by muscle (Wurtman, 1980; Zeisel et al., 1981). Furthermore, serum and brain levels of tryptophan and valine and brain serotonin levels in animals were found to vary in the predicted direction within two hours after a glucose or protein feed so that these changes are rapid.

Serotonin and normal sleep behavior. There are good reasons to believe that brain serotonin influences sleep behavior. Previous work in adult humans, as well as in non-human species, has suggested a relationship between sleep behavior (sleep onset, night waking) and brain serotonin levels (Hartmann, 1977; Koja et al., 1979). Jouvet suggests that serotonergic neurons of the raphé system play a major role in the induction of sleep, since raphé lesions

are followed by insomnia (Jouvet, 1977). Oral administration of l-tryptophan to adults produced consistent significant reductions in sleep latency. No previous studies have been conducted in normal children or infants relating sleep patterns to serotonin levels, tryptophan metabolism, or diet.

In our study, we used observations of infant state as our dependent variable. In order to minimize influences on state other than diet, we had to grapple with diurnal variations, day-to-day developmental changes, as well as wide individual variations, in state behavior. We minimized the impact of diurnal variations by beginning all observations with the evening feeding. We minimized the impact of individual variations by observing each infant after a routine formula feeding, as well as after a modified feeding, so that the routine feeding could serve as a baseline state observation for our treatment effects. Finally, we minimized developmental changes by randomizing and counter balancing the order of feeding routine and modified feedings.

Design

Let me now describe the experiment we designed to investigate whether newborn feedings, modified to influence plasma amino acid ratios and brain serotonin levels, are related to differences in newborn behavioral state.

We chose to compare newborn feedings modified in a manner likely to maximize behavioral differences, yet within the physiological dose range in maternal breast milk. One treatment group received a feed containing tryptophan, 33mg./dl., dissolved in a 10% glucose solution to maximize the carrier transport of tryptophan

across the BBB; the other received a feed containing valine, 50mg./dl. to minimize tryptophan transport, and was dissolved in a 5% glucose solution to make it palatable.

The next slide gives the total amino acid content of the modified tryptophan

Slide 3 about here

and valine formulas which we used. The table also gives the values for Similac 20 and human milk at the top. The tryptophan and valine content of our modified formulas are within the range of the total amino acid present in breast milk and Similac. Amounts are expressed in mg. per liter.

The study design was a randomized double blind experiment in which we compared the effects of a tryptophan feed with those of a valine feed on newborn state behavior.

After obtaining informed consent, 20 healthy fullterm appropriate for gestational age infants were recruited at birth in the nursery and randomly assigned to either the tryptophan or valine feeding conditions. All infants were bottle fed, products of uncomplicated pregnancy, labor, and delivery, and had none or minimal obstetric medications. The next slide shows the sample characteristics.

Slide 4 about here

The randomly assigned groups did not differ on any of these characteristics.

Each infant age 2 or 3 days was fed a modified formula, either tryptophan or valine as assigned, and a routine Similac 20 feeding. The order of feeding regular and modified formulas was randomized and counterbalanced in

the two groups. Both observers and parents were kept blind to the newborns' treatment group.

Each infant was observed continuously for three hours after feeding with recording of the infant's state of consciousness at one-minute intervals. The system for observing newborn state behavior was adapted from the standardized criteria adopted in 1971 and the behavioral definitions can be seen in the next slide. Indeterminate sleep was added and the waking state combines the alert inactive and active states.*

slide 5 about here

Reliability of scoring states among the 5 observers was established at greater than 90% agreement over several 3-hour observation periods prior to data collection. During the study of every fourth infant, a reliability check between two observers simultaneously scoring an infant was performed; agreement ranged between 90 and 95% throughout the study.

Data Analysis and Results

Data were analyzed by computing difference scores for each infant between the modified and regular feeding conditions and then comparing the two groups of infants on the difference scores from each of the dependent variables. The dependent variables included latency to entrance into quiet and active sleep, latency to crying, the duration of time spent in each state and the number of transitions from sleep to waking states. Ten infants were randomly assigned to the tryptophan and valine groups and a 2 group x 2 order (modified feed first, modified feed second) ANOVA was done to analyze the data.

*QS, AS, IS (added), Dr, Wa (combine), Fc

The results showed group differences between the tryptophan and valine groups with no order effects and no group x order interactions. Infants fed tryptophan entered both quiet sleep ($F=10.39$, $p < 0.005$) and active sleep ($F=8.49$, $p < 0.01$) sooner than infants fed valine. The bar graphs on the next two slides show the means and standard errors for the two groups on these two measures.

Slides 6, 7 about here

Infants fed tryptophan showed a trend to spend more time asleep, more time in active sleep ($F=3$, $p < 0.09$), as well as less time in the alert states ($F=3.67$, $p < 0.07$). Furthermore, all newborns displayed the normal newborn pattern of entering sleep through the REM stage. Indeterminate sleep was seen quite rarely and not analyzed.

Heel stick blood samples were obtained on one infant in each treatment group before the feed and after the entire behavioral observation. After the amino acids, tryptophan and LNAA's, were assayed, the ratio of tryptophan concentration to the sum of concentrations of valine, leucine, isoleucine, phenylanine, methionine, and tyrosine was calculated. For each infant, difference scores were computed between the ratio obtained prior to feeding the modified formula and at the end of the observation. The infant receiving the tryptophan feed had a pre-feeding ratio of .096, a post observation ratio of .108, and a difference score of +.012, suggesting that the tryptophan feed minimally increased the ratio. The infant receiving the valine feed had a pre-feeding ratio of .160, a post-feeding ratio of .121, and a difference score of -.039, suggesting that the valine feed minimally decreased the ratio.

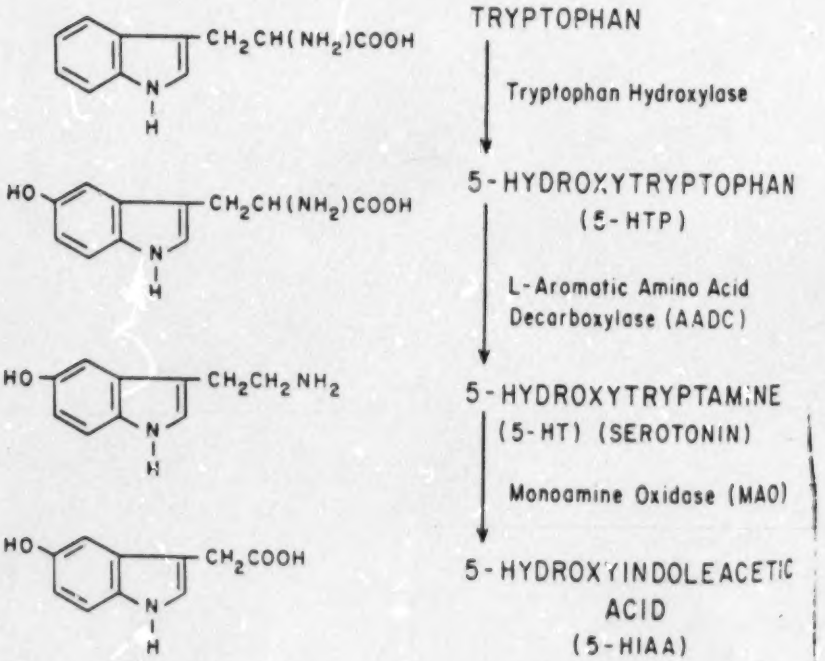
Both effects are in the predicted direction and in keeping with the behavioral effects demonstrated. The behavioral and amino acid data for the modified formula conditions for these two infants are depicted graphically in the next slide.

Slide 8 here

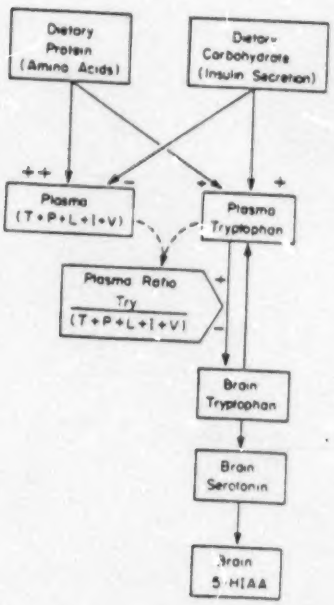
In conclusion, the data suggest that modifying infant feeding preparations with tryptophan and carbohydrate mixtures produces an effect on newborn state behavior without disrupting such state characteristics as mode of onset through active sleep. They suggest that variations in serotonin levels in newborn brains may play a role in modulating the newborn's arousal behavior. Of the various assessments possible of newborn behavior and of the biochemical pathways involved, this work has attempted to relate differences in plasma amino acid ratios with differences in newborn behavioral state. Having demonstrated an effect in this study, it will be necessary to replicate and extend this work. The methodology certainly shows promise for the use of nutrients as independent variables in research on brain-behavior relationships in the developing nervous system. Future work will be necessary to relate these findings to naturally occurring dietary preparations of infant feedings and to developmental changes in state organization.

Slide 1

Synthesis and Metabolism of Serotonin



Slide 2



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Slide 3 - Amino Acid Content of Infant Feeding

TOTAL AMINO ACID CONTENT OF INFANT FEEDINGS

mg per liter

FEEDING	TRP	VAL	LEU	ILE	TYR	PHE	METH	
BREAST MILK	169	608	913	541	0	439	203	*
SIMILAC 20	201	812	1440	754	760	668	467	**
VALINE in D5W	0	354	0	0	0	0	0	***
TRYPTOPHAN in D10W	223	0	0	0	0	0	0	***

NON-PROTEIN AMINO ACID CONTENT OF INFANT FEEDINGS

mg per liter

FEEDING	TRP	VAL	LEU	ILE	TYR	PHE	METH	
BREAST MILK	3	10	6	4	7	2	2	***
SIMILAC 20	0.7	0.7	0.5	0	0.8	0	0	***
VALINE in D5W	0	354	0	0	0	0	0	***
TRYPTOPHAN in D10W	223	0	0	0	0	0	0	***

* Data from Bowes and Church's Food Values of Portions Commonly Used, Pennington and Church, eds., Lippincott, 1980.
** Data from Ross Laboratories, Columbus, Ohio.
*** Data from our own analysis.

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Slide 4

SAMPLE CHARACTERISTICS

	Tryptophan Group		Valine Group	
	$\bar{x}$	SEM (Range)	$\bar{x}$	SEM (Range)
Birth Weight	3446 gms	165.7	3285 gms	71.4
Gestational Age	39.5 wks	0.34	39.2 wks	0.32
Length	50.1 cms	0.9	50.2 cms	0.7
Sex (male)	70%		60%	
Apgar (1 min)	8.3	0.21	8.7	0.26
Apgar (5 min)	9.0	0.10	9.1	0.19
Amount of Modified Feed	2.02 oz.	(1.5-3.0 oz.)	1.77 oz.	(1-2.50 oz.)

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Slide 5

Definition of States

1. Quiet sleep: This is a state of behavioral quiescence. The eyes are firmly closed and still; there is little or no fine motor activity with the exception of occasional sighs, startles or rhythmic mouthing, and respiration is relatively slow and regular and abdominal.

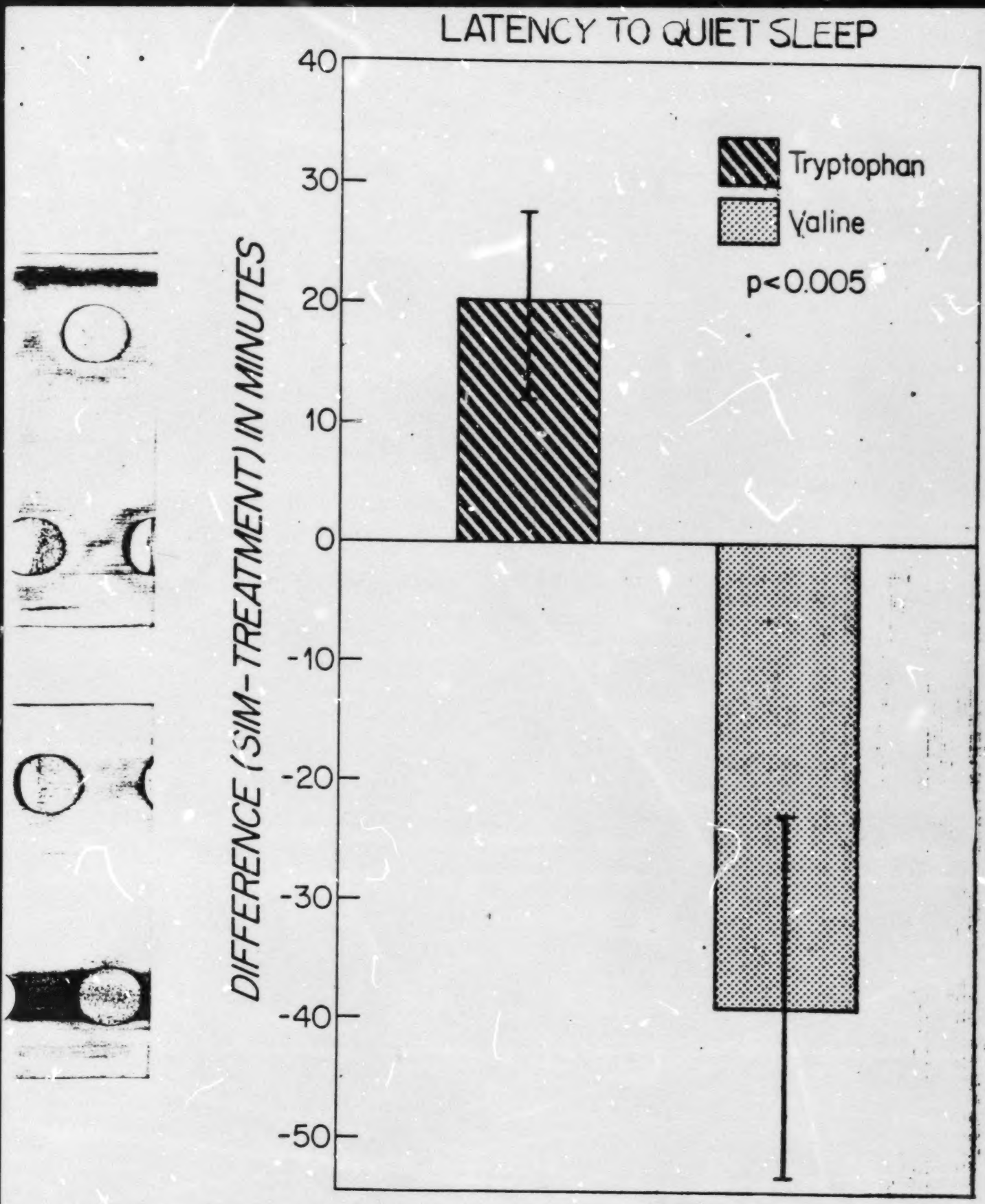
2. Active sleep: This is a state of considerable behavioral activity. The infant's eyes are closed and rapid eye movements may be present, sometimes with brief eye opening. Respiration is irregular in amplitude, faster in rate, and primarily costal in nature. Sporadic localized or generalized twitching and motor movements occur frequently, usually slow and writhing, occasionally sudden and jerky. Facial movements consist of grimacing, smiling, sneering, frowning, pouting and bursts of sucking.

3. Indeterminate sleep: Episodes of sleep which do not meet either of the above criteria.

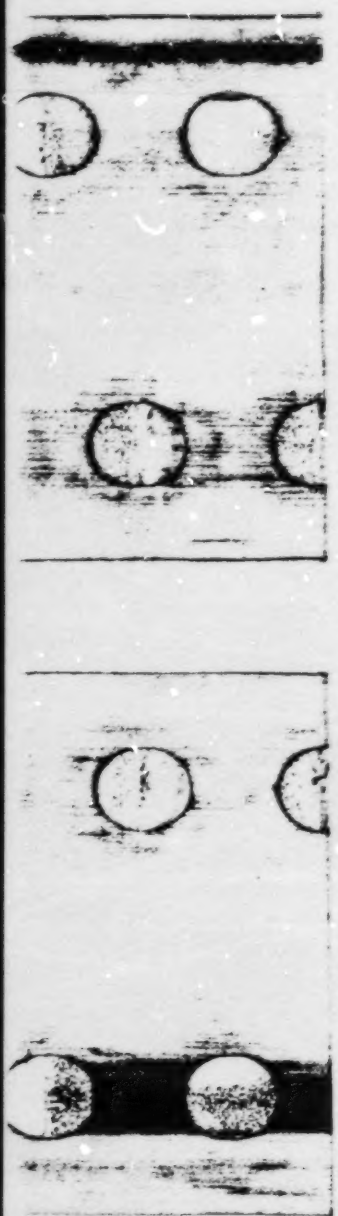
4. Drowsy: The infant's eyes may be open, or slowly closing and opening; when open, the eyes are dazed in appearance and respiration is fairly regular and levels of motor activity are low.

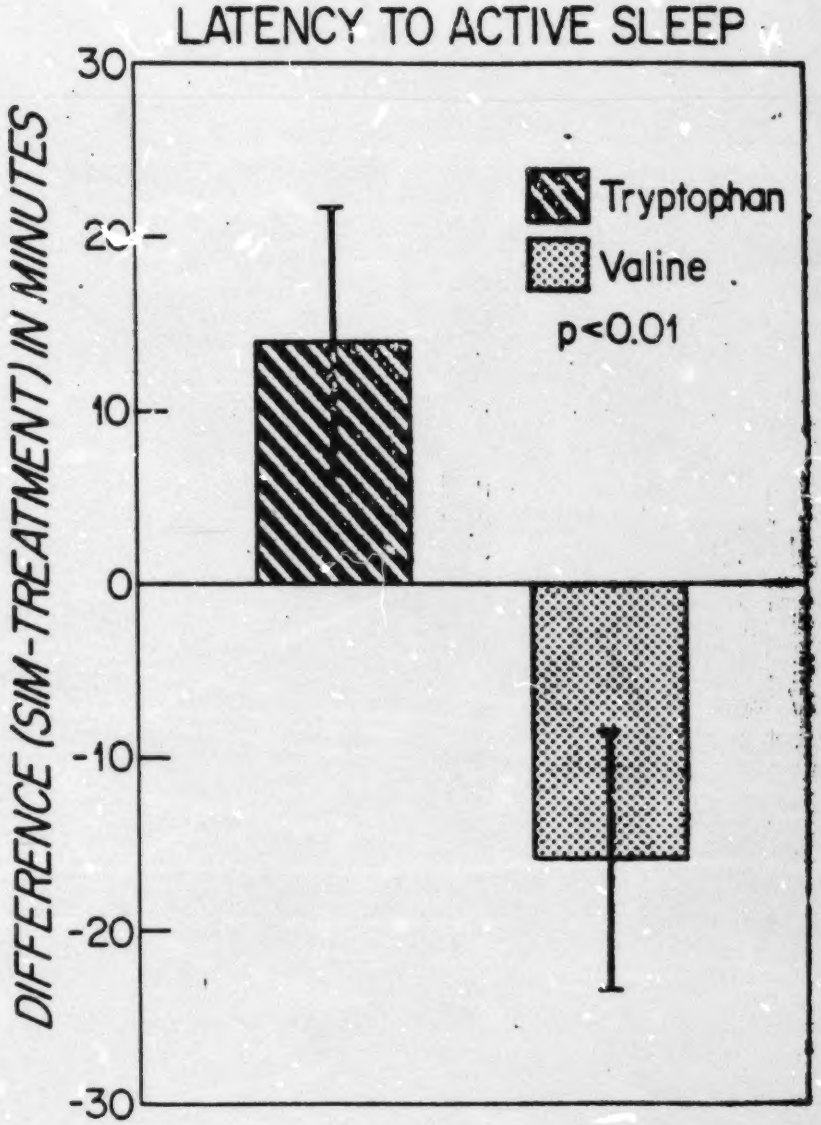
5. Wakefulness: The eyes are alert and scanning, and the body is relatively quiet and inactive, but there may be considerable motor activity.

6. Fuss or cry: Generalized motor activity is present together with two or more cry bursts or short fuss vocalizations. Eyes may be closed during hard crying


LATENCY TO QUIET SLEEP
DIFFERENCE (SIM-TREATMENT) IN MINUTES
40
30
20
10
0
-10
-20
-30
-40
-50
Tryptophan
Valine
p<0.005

Slide 6




LATENCY TO ACTIVE SLEEP
DIFFERENCE (SIM-TREATMENT) IN MINUTES
30
20
10
0
-10
-20
-30
Tryptophan
Valine
p<0.01

Slide 7

Slide 8

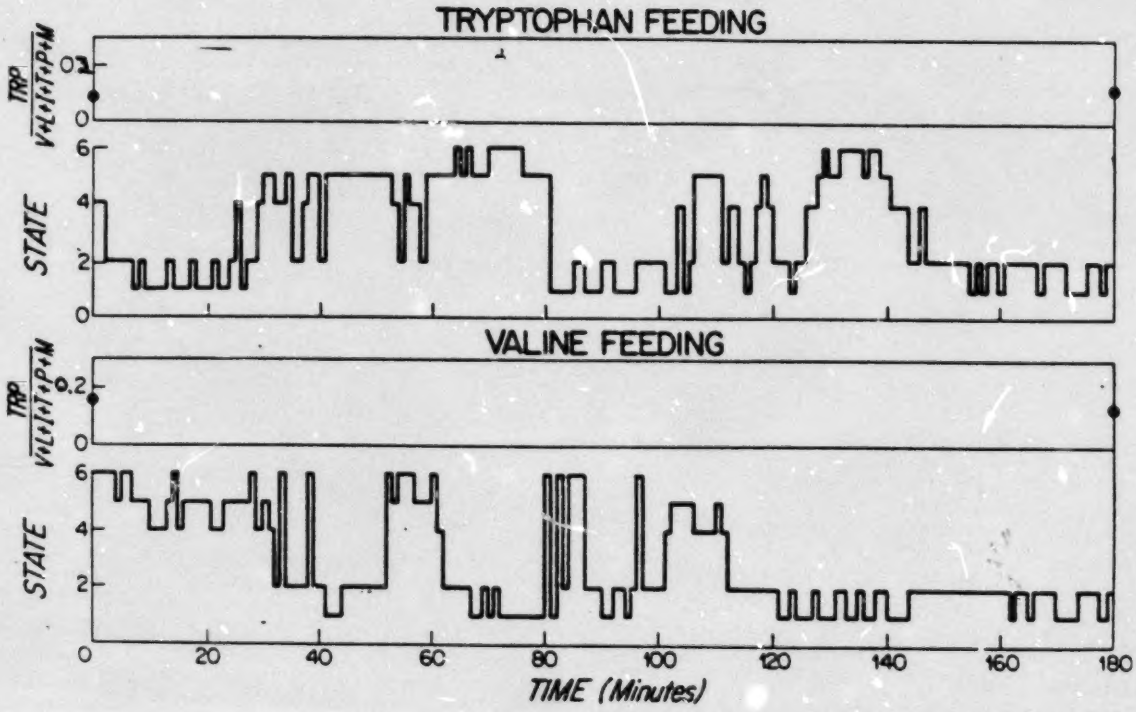


Figure 1. Behavioral state and plasma amino acid ratios for newborns during the 180 minutes after tryptophan-modified feed (top) and valine-modified feed. State numbers refer to states described in Table 2: 1=QS, 2=AS, 3=IS, 4=Dr, 5=Wa, 6=FC. Plasma amino acid ratios are shown above the state data and are expressed in the ratio of Trp to V + L + I + T + P + M in n moles.